CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-189

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

ANDA: 75-189

DRUG PRODUCT: Nabumetone Tablets, 500 mg and 750 mg

FIRM: Teva Pharmaceuticals USA

DOSAGE FORM: Oral Tablet

STRENGTH: 500 mg and 750 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER acceptable on 09/22/98

BIO STUDY: Acceptable (Bio review was dated 08/06/98). The recommended disolution specifications are as follows:

> The dissolution testing should be conducted in 900 mL of 2% SLS, at 37° C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less tha of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

VALIDATION: Both the drug substance and drug product have no USP monographs. Philadelphia District Laboratory has performed the method validation. TEVA has provided satisfactory response to the District's comments on their methods via a telephone amendment (dated 02/22/00) to the ANDA.

STABILITY: Three months room temperature condition data in the market package size, 60s, 100's and 1000's, are provided. (note: 18 month and 20 month CRT dissolution stability data obtained by DOB's recommended specs and method for the 500 mg strength and the 750 mg strength product, respectively, are provided). The container/closure system used for the stability study is equivalent to the system proposed for commercial use (note: Phillips Marlex 5502BN resin will be used in the future for the bottles. Technical data are provided and equivalency of the container/closure system has been established). All reported data are within specifications as listed. A 24 month expiration date is proposed.

Stability tests and specifications are as follows:

> **Assay:** 90.0-110.0% (method SI-11125)
> **Dissolution:** NLT in 45 min. (method SI-11069)
> **Impurities/degradation products** (method SI-11125):

Any individual
Total:NMT (method SI-11125)
Appearance (method SI-2000):
500 mg strength: White, oval-shaped, film coated tablets.
750 mg strength: Beige, oval-shaped, film coated tablets.

LABELING: Labeling Approval Summary was signed off on 05/05/00.

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch: Teva manufactured two test batches: #K-22174 (750 mg tablets) and #K-22264 (500 mg tablets). Lot# K-22174 was used for in-vivo studies. Both test batches were used for in vitro studies.

The sizes for ANDA test batches and production batches are summarized as follows:

Nabumetone Tablets	Test Batch Size	Production Batch Size
500 mg (Tablet wt: 660 mg)		
750 mg (Tablet wt: 990 mg)		

SIZE OF STABILITY BATCHES: Two test batches: #K-22174 (750 mg tablets) and #K-22264 (500 mg tablets) were placed on stability studies.

PROPOSED PRODUCTION BATCHES: The proposed production batch size are presented above. The manufacturing process for production batches is the same as that for test batches.

Review Chemist: S.H. Liu **DATE:** 05/09/00
Shing H. Liu, Ph.D.

Team Leader: DS Gill **DATE:** 5-11-00
Devinder Gill, Ph.D.

V:\Firmsnz\teva\ltrs&rev\75189app.sum

RECORD OF TELEPHONE CONVERSATION

The firm was contacted regarding comments the Philadelphia District Lab had concerning the methods validation (see attachment for the specific comments)

The firm agreed to address these comments.

Their response will be submitted as a Telephone Amendment to Ruby Yu (301) 594-0180 as well as a fax and hard copy to the document room (Document Room Fax number (301) 827-4337).

DATE
February 10, 2000

ANDA NUMBER
75-189

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Nabumetone

FIRM NAME
Teva Pharmaceuticals USA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Deborah A. Jaskot

TELEPHONE NUMBER
215-256-8400

SIGNATURE
Dave Gill
Shing Hou Liu
Ruby Yu

Ruby Yu 2/11/00

V:\FIRMSNZ\TEVA\TELECONS\75189.tc.021000.doc

CC: T-Con Binder Log
ANDA 75-189

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
PHILADELPHIA DISTRICT
SCIENCE BRANCH

MEMORANDUM

DATE: 23 March 1999

FROM: Director, Science Branch
Philadelphia District, HFR-CE160

SUBJECT: ANDA 75-189: Nabumetone Tablets, 750 mg, and Drug Substance
Teva Pharmaceuticals USA, Sellersville, PA 18960
RE: 40061

TO: Shing H. Liu, Ph.D.
CDER, Office of Generic Drugs, Div. Of Drug Chemistry I, HFD-623

The Philadelphia District Laboratory performed the analysis of Nabumetone Tablets, 750 mg, and Drug Substance using the firm's method and samples provided. Attached are the summary of results, worksheets, and comments for the subject ANDA.

The following comments should be considered before approval of the method:

Although all test results were within the firm's specifications, the method specifies no relative standard deviation limits for replicate injections for the drug substance assay and related substance determinations for the drug substance. The analyst did perform six replicate injections and obtained R.S.D. of respectively. It is recommended that these determinations incorporate an R.S.D. specification with an appropriate value, such as not more than

Similarly for the dosage form, an R.S.D. of 10% is specified for the impurities and degradation products determination (Standard Solution C). As the analyst obtained an actual R.S.D. of 0.12%, a lower specification seems appropriate, such as not more than

Based on the analytical results, the ANDA method appears to be suitable for regulatory control of this product, but the comments above should be considered before final approval of the ANDA. No other problems were encountered with the analytical methods.

W. Charles Becoat

RECORD OF TELEPHONE CONVERSATION

I called D. Jaskot and informed her that their 2/3/99 submission submitted as a PAC-ATLS supplement was not appropriate for an application in TENTATIVE approval status. Since we also do not want a regular amendment submitted in response to our TA letter (which would reopen the application considerably prior to expiration of patent), I suggested the proposed addition of an alternate test site be submitted as a GRATUITOUS amendment.

Ms. Jaskot said she understood the situation and would resubmit the information as a gratuitous amendment.

X:\new\firmsnz\teva\telecons\75189.001

DATE
2/8/99

APPLICATION NUMBER
75-189

TELECON

INITIATED BY FDA

PRODUCT NAME
Nabumetone Tablets 500 mg and 750 mg

FIRM NAME
TEVA

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Deborah Jaskot
DRA

TELEPHONE NUMBER
215-256-8400

SIGNATURE
Mark Anderson

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT: **TEVA Pharmaceuticals USA**

DATE OF SUBMISSION: **February 9, 1999**

TELEPHONE NO. (Include Area Code): **(215) 256-8400**

FACSIMILE (FAX) Number (include Area Code): **(215) 256-8105**

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License Number if previously issued):
1510 Delp Drive
Kulpsville, PA 19443

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, and ZIP Code telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously issued): **75-189**

ESTABLISHED NAME (e.g., Proper name, USP/USAN name): **NABUMETONE TABLETS**

PROPRIETARY NAME (trade name) IF ANY: **N/A**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any): **4-(6-methoxy-2-naphthalenyl)-2-butanone**

CODE NAME (If any)

DOSAGE FORM: **TABLET**

STRENGTHS: **500 mg and 750 mg**

ROUTE OF ADMINISTRATION: **ORAL**

PROPOSED INDICATION(S) FOR USE: **Acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis**

APPLICATION INFORMATION

APPLICATION TYPE

(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ■ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGIC APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: **RELAFEN ®** Holder of Approved Application: **SMITHKLINE BEECHAM**

TYPE OF SUBMISSION

(check one) ☐ ORIGINAL APPLICATION ■ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (eg. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5))
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification
	17. Field copy certification
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of Contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71 , 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The date and information in this submission have been reviewed and are certified, to be true and accurate.

Warning: a willfully false statement is a criminal offense, U. S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Deborah Jaskot	**Deborah A. Jaskot** **Senior Director, Regulatory Affairs**	2/9/99

ADDRESS (Street, City, State and ZIP Code)	Telephone Number
TEVA Pharmaceuticals USA **1510 Delp Drive, Kulpsville, PA 19443**	**(215) 256-8400**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing Instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a current valid OMB control number.

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (4/97)

ATTACHMENT 1

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
FAX: (215) 256 7855

ANDA 75-189

NABUMETONE TABLETS, 500 mg and 750 mg

GRATUITOUS AMENDMENT -
ADDITION OF ANALYTICAL TESTING FACILITIES

In accord with the 21 CFR 314.96(b), TEVA Pharmaceuticals USA hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Division of Emergency Investigations Operations.

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

2/9/99
Date

TEVA PHARMACEUTICAL INDUSTRIES LTD.
P.O.BOX 353 KFAR SABA 44102 ISRAEL TEL. 972-9-7648222 FAX. 972-9-7656889

cGMP CERTIFICATION

TEVA Group , Manufacturing Operations Division, certifies that, to the best of our knowledge, all stability testing, performed at:

TEVA Pharmaceutical Industries Ltd.
2, Hamarpeh Street
Post Office Box 1142
Jerusalem 91010, Israel

are in compliance with current Good Manufacturing Practice in accordance with 21 CFR parts 210 and 211.

The laboratory was inspected by the FDA in November 1997. No 483 was issued.

Signature: _____ Date: September 23, 1998

Gil Bismuth
Director, Quality Assurance
Pharmaceutical Operations Division &
Corporate R&D Division

TEVA PHARMACEUTICAL INDUSTRIES LTD.
P.O.BOX 353 KFAR SABA 44102 ISRAEL TEL. 972-9-7648222 FAX. 972-9-7656889

cGMP CERTIFICATION

TEVA Group , Manufacturing Operations Division, certifies that, to the best of our knowledge, all stability testing, performed at:

Abic,
TEVA Pharmaceutical Industries Ltd.
Post Office Box 8077
Kiryat Nordau Industrial Zone
Netanya, Israel

are in compliance with current Good Manufacturing Practice in accordance with 21 CFR parts 210 and 211.

The laboratory was inspected by the FDA in November 1997. No 483 was issued.

Signature: _____ Date: September 23, 19[illegible]

Gil Bismuth
Director, Quality Assurance
Pharmaceutical Operations Division &
Corporate R&D Division

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-189 Date of Submission: August 18, 1997

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Nabumetone Tablets, 500 mg & 750 mg

Labeling Deficiencies:

1. CONTAINER - 60's, 100's & 1000's

   We encourage you to differentiate the two different strengths from each other by using contrasting colors and/or boxing, or any other means.

2. INSERT

   a. DESCRIPTION

      i. Third paragraph:

         A) First sentence:

            Each tablet, for oral administration, contains ...

         B) Second sentence:

            In addition, each tablets contains the following inactive ingredients: colloidal ...

   b. CLINICAL PHARMACOLOGY

      We encourage the inclusion of "6-methoxy-2-naphthylacetic acid (6MNA)" underneath the structural formula.

   c. INDICATIONS AND DOSAGE

      Nabumetone tablets are indicated ...

   d. PRECAUTIONS

      Replace "children" with "pediatric patients" in

two places.

e. ADVERSE REACTIONS (Incidence <1%--Probably Causally Related) - Genitourinary:

Delete "*nephrotic syndrome*" from the list.

f. DOSAGE AND ADMINISTRATION - Penultimate sentence:

Nabumetone tablets can be ...

g. HOW SUPPLIED

i. Please include the term "unscored" if your products are not scored. If scored, include the scoring information in the description of your drug products.

ii. We encourage the inclusion of NDC numbers.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed container labels and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the last submitted labeling with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

TELEPHONE MEMO

To: Bill North for Deborah Jaskot
(215) 256-8400 X 5249

REF # ANDA 75-189

From: Lizzie Sanchez

Date: 12/1/97

Subject: **Nabumetone Tablets 500 and 750 mg**

Requested by: Andre Jackson

The firm was requested to submit all chromatograms which show an interfering peak near the major analyte,6-methoxy-2-naphthylacetic acid, as was observed with subject #5. Please submit the chromatograms above specified for both fasting and non-fasting studies. Please label "Bioequivalence telephone amendment".